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Multiple System Atrophy Following Chronic Carbon Disulfide Exposure

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Carbon disulfide toxicity is well characterized. The principal target organ is the nervous system, although cardiovascular, reproductive, ophthalmologic, and other effects are also recognized. The neurotoxicity manifests in three ways: encephalopathy, peripheral and cranial nerve dysfunction, and movement abnormalities. This report describes a case of olivopontocerebellar atrophy, a form of multiple system atrophy, developing in an adult after over 30 years of occupational exposure to carbon disulfide. The patient presented with the insidious onset of balance problems, impotence, and irritability, without tremor, cogwheel rigidity, bradykinesia, or changes in facial expression. Over the next few years severe ataxia developed, and the clinical diagnosis was confirmed with computed tomography and magnetic resonance imaging scans. The patient experienced multiple medical complications and died approximately 9 years after diagnosis. This case is consistent with a large body of clinical and experimental literature, much of it 50 years old, showing that carbon disulfide can cause movement disorders. It also serves as a reminder that movement disorders, ranging from parkinsonism to dystonia, are associated with a variety of toxic exposures such as manganese, carbon monoxide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, and medications. *Key words*: carbon disulfide, cellulose, environmental diseases, movement disorders, multiple system atrophy, occupational diseases, olivopontocerebellar atrophy, rayon, textiles. *Environ Health Perspect* 106:611–613 (1998). [Online 18 August 1998].
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Carbon disulfide is a clear, colorless volatile solvent used in manufacturing viscose rayon, rubber, cellophane, carbon tetrachloride, and pesticides; as a fumigant; and in other applications. A wide range of toxic effects, including cardiovascular, ocular, and reproductive effects, has been well recognized for over a century (*1–4*). The nervous system, however, is the principal target organ of carbon disulfide.

There are three principal manifestations of carbon disulfide neurotoxicity: acute and chronic encephalopathy, peripheral and cranial neuropathy, and movement disorders. The major focus of recent literature has been on encephalopathy following low-level exposures. This syndrome includes subjective symptoms such as headache and vertigo and changes in affect and cognition (*5–7*). Movement disorders have received much less attention. This paper presents a case of multiple system atrophy developing after long-term exposure to carbon disulfide.

Case Presentation

The patient first presented at approximately 60 years of age with slowly progressive balance problems, impotence, irritability, and emotional lability. His balance and coordination worsened until, by age 62, he had difficulty with walking, manual dexterity, and speech. He also noted severe nightmares. There were no tremors, no changes in facial expression, no cogwheel rigidity, no bradykinesia, and no impairment of hearing or vision. A magnetic resonance image (MRI) at age 63 gave equivocal results (variously interpreted as normal or mild cerebellar atrophy), but a repeat MRI a year later showed definite cerebellar and brainstem atrophy. Thyroid function, urinary lead and mercury levels, serum vitamin B_{12} levels, and electroencephalography were normal.

At age 64, the patient was evaluated by a neurologist. Blood pressure was 160/80 without orthostatic changes; speech was slightly slurred; cognition and affect were generally intact; and cranial nerve function was normal. Motor examination revealed normal strength without involuntary movements, but with rippling movements of large muscles in the chest and lower extremities. There were impairments of finger-to-nose, heel-knee-shin, and rapid alternating movements. The patient was unable to tandem walk and was unstable when standing with his feet close together, even with his eyes open. Deep tendon reflexes were normal, and no pathological reflexes were present. A computed tomography (CT) scan showed atrophy of the cerebellar and pontine regions. He was diagnosed with olivopontocerebellar atrophy of the sporadic type.

In the next few years, the patient experienced progressive deterioration in function. Dysphagia, dysarthria, and ataxia increased. By age 67 he had become unable to walk and had little functional independence. He also suffered multiple medical complications including rectal bleeding, neurogenic bladder with chronic urinary infections requiring intermittent catheterization, a fungal infection of the mouth, peptic ulcer disease, bronchitis with dysphagia, gynecomastia (probably secondary to ranitidine use), and hiccups. A repeat MRI of the brain at age 68 (see Fig. 1) showed advanced cerebellar atrophy and prominent atrophy in the posterior tracts and nuclei of the pons. The patient died at the age of 69. No autopsy was performed.

Previous medical history was remarkable only for benign positional vertigo, hiccups, some orthostatic hypotension, peptic ulcer disease, and prostatic hypertrophy. The patient had completed high school. He was a lifelong nondrinker and nonsmoker.

The patient had been employed from age 25 to age 59 in a plant that produced viscose rayon. During most of this time, he worked in the spinning room. Although measured air levels of carbon disulfide from his plant were not available, the spinning room has been reported to pose some of the highest carbon disulfide levels in rayon manufacturing (*8*), ranging from 10 to 20 ppm (31–62 mg/m^3) and sometimes reaching 30 ppm (93 mg/m^3) or higher (*9–13*).

Discussion

Olivopontocerebellar atrophy belongs to the multiple system atrophy family of neurologic

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disorders (*14,15*). This complex is characterized by autonomic dysfunction, parkinsonism, and ataxia, which may occur in any combination. Common findings include bradykinesia with rigidity, tremor, or both (poorly responsive to levodopa therapy); cerebellar or corticospinal signs; orthostatic hypotension; impotence; and urinary incontinence or retention. A predominance of parkinsonism is termed striatonigral degeneration, while a predominance of autonomic dysfunction is termed Shy-Drager syndrome. When cerebellar dysfunction predominates, as in the present case, the term olivopontocerebellar atrophy is used.

In these disorders several parts of the brain, many of them involved in motor activity, are affected by neuronal loss and gliosis, including the neostriatum, the substantia nigra, the globus pallidus, the cerebellum, the inferior olives, the basis pontine nuclei, the intermediolateral horn cells, the anterior horn cells, and the corticospinal tracts. Oligodendroglial tangle-like inclusions, called glial cytoplasmic inclusions or oligodendroglial microtubular tangles, are a common pathologic finding (*15*). While olivopontocerebellar atrophy is distinguished from the other types of multiple system atrophy by the relative prominence of ataxia, there can be considerable parkinsonism as well, especially in the sporadic (as opposed to the familial) form. The most common parts of the brain affected are the olives, pons, and cerebellum, as well as the striatum and substantia nigra (*16*).

Clinical accounts of movement disorders among carbon disulfide workers, dating from at least as far back as the 1930s, have described tremor, involuntary movements, and parkinsonism (*3,17–23*). More recently, Peters et al. (*24*) described a syndrome of atypical parkinsonism, cerebellar signs, hearing loss, and sensory changes in 21 workers with carbon disulfide exposure. Ataxia was present in 8 of the 21 workers. In a study of 16 workers with long-term carbon disulfide exposure, Aaserud et al. (*6*) found that the most common clinical abnormality (appearing in eight individuals) was coordination deficit. Two of the patients in this study had visible cerebellar atrophy on CT scans. Huang et al. (*25*) reported a detailed neurologic investigation of 10 patients with "polyneuropathy and various neuropsychiatric symptoms" following carbon disulfide exposure. In four cases, brain MRI revealed lesions of the basal ganglia and corona radiata.

Pathological findings in humans following carbon disulfide exposure have only rarely been reported. They include neuronal degeneration diffusely over the cerebral cortex, globus pallidus, and putamen, and a decrease in Purkinje cells in the cerebellar cortex (*26,27*).

Animal studies demonstrate clinical and pathological changes that correspond to these human observations. In dog and cat studies, carbon disulfide exposure led to a syndrome of ataxia, tremor, myoclonic jerks, spasticity, muscular atrophy, and aggressive behavior (*26,28*); pathological damage was seen in the frontal cortex, caudate, putamen, and Purkinje cell layer. Richter (*29*) exposed rhesus monkeys to carbon disulfide; they developed an extrapyramidal syndrome with flexor dystonia, slowness of movement, rigidity, and tremor. The globus pallidus and substantia nigra were the most severely affected parts of the brain, while the cortex was relatively spared. In more recent rat studies, dose-related gait abnormalities were the first manifestation of exposure, although this may have reflected peripheral nerve toxicity rather than extrapyramidal effects (*30*). Pathological findings were not reported. Other work on rats has helped clarify the mechanisms of carbon disulfide axonal toxicity (*31*), but it is not clear if these findings can be applied to the cerebellum or extrapyramidal pathways.

Carbon disulfide exposure is primarily a workplace concern, and ambient environmental exposures are ordinarily low (*4*). However, ambient environmental exposures may occur. In 1996, 137 facilities in the United States reported carbon disulfide emissions to the EPA Toxics Release Inventory. At the viscose rayon plant that employed this patient, combined fugitive and stack emissions of carbon disulfide totaled 33.4 million pounds in 1995 and 27.7 million pounds in 1996—nearly 50 tons each day (*32*). In addition to these ongoing emissions, acute releases of carbon disulfide during transport remain a possibility. There is at least one report of cerebral damage following a single exposure to carbon disulfide (*33*). Therefore, environmental exposure to carbon disulfide, although rare, remains a concern.

This case also serves as a reminder that movement disorders may result from other environmental exposures. Manganese causes a parkinsonian syndrome (*34,35*). This is especially worrisome in view of two recent disclosures: the very high prevalence of parkinsonian symptoms among the elderly (*36*) and the possible impending increase in

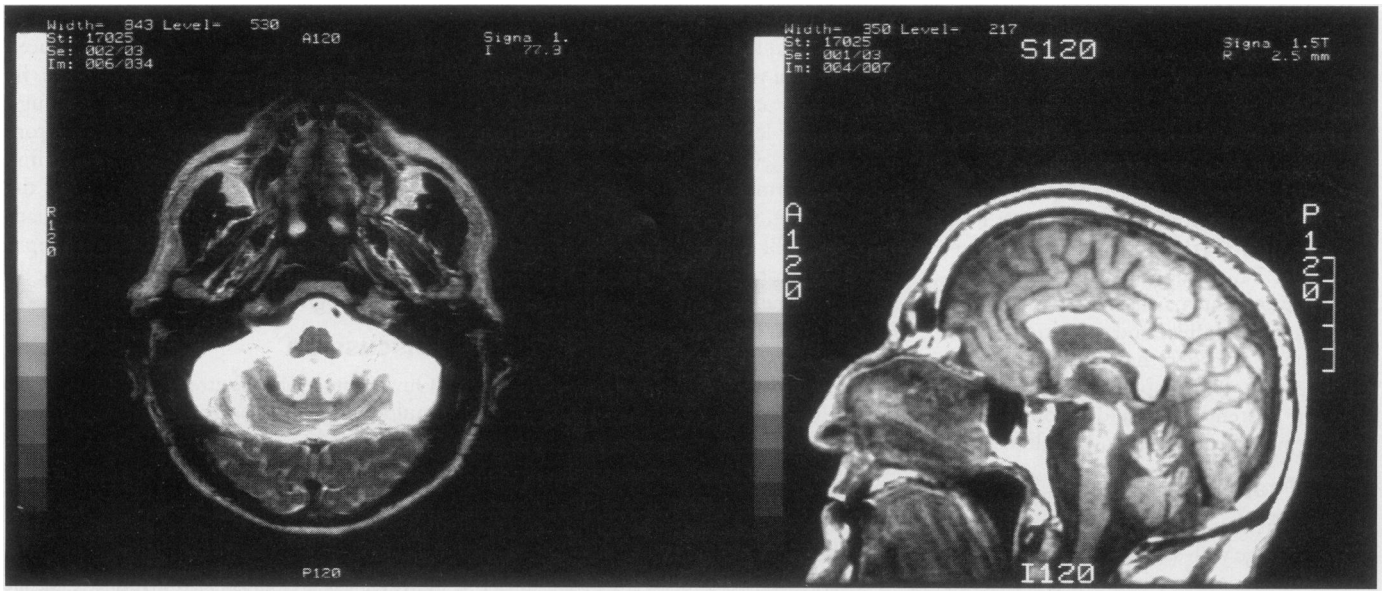

Figure 1. Magnetic resonance image showing olivopontocerebellar atrophy in a patient who had been occupationally exposed to carbon disulfide for over 30 years.

environmental manganese exposure due to the use of methylcyclopentadienyl manganese tricarbonyl in gasoline (*35*). Acute high-level exposures to carbon monoxide and perhaps methanol can cause residual parkinsonism (*34*), and lightning and electrical injuries have been reported to cause dystonia, choreoathetosis, myoclonus, and other movement disorders (*37*). A variety of medications can cause dyskinesias (*38*), and the major experimental model of parkinsonism, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was discovered as a contaminant of drugs of abuse (*39*). Thus, environmental and occupational exposures can cause a variety of movement disorders.

Conclusion

This patient presented with olivopontocerebellar atrophy following over 30 years of high-level exposure to carbon disulfide. While this association has not previously been reported, it is clinically and pathologically consistent with a range of movement disorders seen in the setting of occupational carbon disulfide exposure.

Industrial exposures to carbon disulfide have decreased in industrialized nations in recent years as a result of heightened awareness of the solvent's toxicity, enclosure of some production processes, improvements in ventilation, and replacement of carbon disulfide by other agents. However, carbon disulfide continues to be an important industrial chemical. High occupational exposures still occur, especially in developing nations, and environmental exposures may occur as well. Clinicians should be alert to the possibility of movement disorders among patients with carbon disulfide exposure, in addition to the better recognized toxic manifestations of this chemical. Clinicians should also be aware of the potential of other environmental exposures to cause movement disorders.

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